AIDS FUNDING

MicroGeneSys Vaccine Trial Gets A Public Peer Review

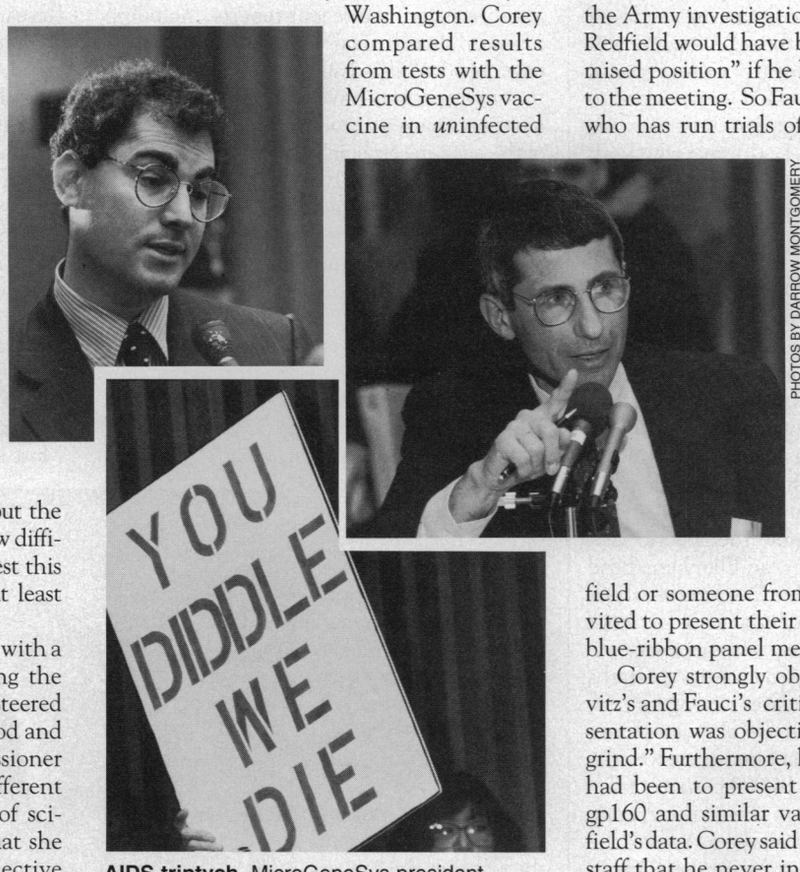
When Congress gave $20 million to the Defense Department last month for a large-scale test of a therapeutic AIDS vaccine made by the Connecticut biotech firm MicroGeneSys, the AIDS research establishment was outraged. National Institutes of Health (NIH) Director Bernadine Healy, along with many top AIDS researchers, branded the unusual appropriation a blatant attempt to circumvent peer review. In response, Healy quickly named a blue-ribbon panel of scientists, activists, and NIH administrators to discuss the proposed trial. Last week, the panel met for the first time on the NIH campus and, surrounded by placards and television cameras, carried out a very public and unwieldy form of peer review.

The panel didn't reach any consensus about whether the MicroGeneSys vaccine—gp160—should be tested in a large-scale trial. Indeed, it didn't reach consensus on much of anything, and many researchers present said they were frustrated by the rambling 5-hour colloquy. But even though the first session of the blue-ribbon panel didn't finish its task—another meeting is promised soon—it did serve to highlight how little is now known about the efficacy of therapeutic vaccines and how difficult it's going to be to decide how to test this promising strategy for preventing or at least delaying the symptoms of AIDS.

Though Healy opened the meeting with a few quick jabs at Congress for passing the $20 million appropriation, she quickly steered the 32 panel members—including Food and Drug Administration (FDA) Commissioner David Kessler and directors of three different branches of NIH—in the direction of science rather than politics, stressing that she wanted the panel to "give gp160 an objective and fair assessment."

Dan Hoth, head of the Division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID), provided some of the background needed for such an assessment. Hoth noted that since 1989, trials of MicroGeneSys's gp160 have involved more than 1000 people infected with HIV. Preliminary results show the vaccine is safe and that it can broaden an infected person's immune response. But those results don't show whether gp160 can actually prevent the development of AIDS symptoms. To find out whether it can, Lt. Col. Robert Redfield of the Walter Reed Army Institute of Research and his co-workers are running a 600-person, placebo-controlled trial. Redfield, however, is under investigation by the Army following allegations that he overstated the significance of preliminary results of gp160 trials (*Science*, 6 November, p. 883)—and he was not present at the panel meeting.

Consideration of the MicroGeneSys vaccine took on a considerably sharper tone in the presentation of the speaker who followed Hoth: Lawrence Corey of the University of Washington. Corey compared results from tests with the MicroGeneSys vaccine in *un*infected people to similar tests with preventive vaccines from two other companies and said that by the criterion he used—functional antibody responses—the MicroGeneSys preparation did not look as promising. Corey also noted some discouraging data from mouse experiments related to the MicroGeneSys vaccine. Though those results came from tests of gp160 in its role as a potential preventive vaccine, Corey used them to question the MicroGeneSys vaccine's promise as a therapeutic agent. He also raised the possibility that vaccinated people in the early, uncontrolled Redfield trials who had a slowed decrease of their CD4 cells—critical players in the immune system that HIV selectively destroys—might have had the same response without the vaccination.



PHOTOS BY DARROW MONTGOMERY

AIDS triptych. MicroGeneSys president Volvovitz *(upper left)*, NIH's Fauci, AIDS activist at the recent blue-ribbon panel meeting.

MicroGeneSys president Franklin Volvovitz, who was in the audience, criticized Corey's summary as possibly "biased" and "misleading." Volvovitz also questioned why Redfield was not there to present his own data. And Volvovitz wasn't mollified when NIAID Director Anthony Fauci explained that the scientific data would be discussed more thoroughly at future panel meetings. Volvovitz's reply was that "election year politics have certainly established that whatever you say up front sticks."

Later, Fauci told *Science* that because of the Army investigation, he was worried that Redfield would have been put "in a compromised position" if he had presented his data to the meeting. So Fauci says he asked Corey, who has run trials of both preventive and therapeutic AIDS vaccines, to give an overview of Redfield's data. But, in Fauci's view, Corey "did not do that." Though Fauci had no criticism of the data Corey presented, he said he was concerned that Corey had focused on comparing preventive and therapeutic vaccines rather than concentrating on Redfield's data. Fauci said Redfield or someone from his group will be invited to present their data the next time the blue-ribbon panel meets.

Corey strongly objected to both Volvovitz's and Fauci's criticisms. He said his presentation was objective—"I have no ax to grind." Furthermore, he said, his assignment had been to present the relevant data on gp160 and similar vaccines—not just Redfield's data. Corey said he made clear to Fauci's staff that he never intended to comprehensively review Redfield's findings, which, in any case were included in a briefing book supplied to the panel. Corey said the comparison of preventive and therapeutic vaccines "has some relevance." When all the available related products are examined, he asked, "is this [MicroGeneSys] vaccine special? The data clearly supports: no."

The purpose of the meeting, however, wasn't simply to discuss gp160—it was to consider how best to test the available therapeutic AIDS vaccine candidates. Most researchers think a trial in which many experimental preparations are compared is preferable to the congressionally mandated large-

scale trial of gp160 alone. As a step in this direction, NIAID announced at the meeting that it plans to begin small trials next spring that pit the MicroGeneSys vaccine against those made by California biotech companies Chiron and Genentech. The trials will focus on safety and on the ability of the vaccines to stimulate immune responses. But small trials like those, which gather data primarily on "surrogate markers" of AIDS progression (such as changes in CD4 cell counts and the amount of HIV in a patient's system) will not answer the question of whether a therapeutic AIDS vaccine can extend life. Answering that question, say many AIDS researchers, will require larger trials that measure "clinical endpoints," such as development of specific opportunistic infections or death.

Yet before starting such a large-scale trial, researchers would like convincing surrogate marker data indicating that the vaccine will work. And from the "purisitic" vantage point, Fauci told the meeting, the scientific data do not yet meet that requirement. But scientific considerations clashed at the meeting with the demands of AIDS activists, who want access to therapeutic vaccines. Against a backdrop of signs saying "You diddle, we die" and "MicroGeneSys is not the enemy," AIDS activist and panelist Mark Harrington argued that "there is nothing else on the horizon, and this is a precious opportunity...to really answer the question, once and for all, with clinical endpoints, whether this approach is going to pay off."

The panelists were responsive to this point of view and spent much of the meeting discussing the merits of a "large, simple trial" that would compare a few therapeutic vaccines. As described by Susan Ellenberg, head of biostatistics at NIAID's Division of AIDS, such a placebo-controlled trial would attempt to assess only one measure: whether a vaccine could reduce AIDS-related illnesses or deaths by one-third. Because it takes so long for people with HIV infection to develop symptoms, it would take 30,000 patients to answer the question in 2 years—or 14,000 patients in 5.

If a large, simple trial of several therapeutic AIDS vaccines results from the furor over the $20 million appropriation, several AIDS activists would be satisfied. David Gold of the Gay Men's Health Crisis said that he would like to think that "much good" could stem from a "sleazy action." But, in the minds of many researchers who were disappointed by the lack of focus at the meeting, there's a long way to go, scientifically, to reach that goal. At the panel's next meeting, scheduled for 23 November, Fauci promises a fuller discussion of scientific issues. And that's none too soon. Healy, Kessler, and the secretary of defense—who jointly have oversight of the large-scale test of the MicroGeneSys vaccine—by law only have until April to speak their minds.

–Jon Cohen

CANCER RESEARCH

Closing In On Melanoma Susceptibility Gene(s)

As the hot summer sun fades to a distant memory and the winter chill sets in, concern about malignant melanoma, a cancer often connected with excessive sunbathing and its accompanying ultraviolet radiation, may go into hibernation for most people. But when spring break rolls around, health columns in newspapers and magazines will again be filled with articles about the dangers of America's obsession with a "healthy" suntan. In the scientific world, however, melanoma is a topic for all seasons, and recent reports, including a powerful statistical analysis published on page 1148 of this issue of *Science*, indicate that investigators have drawn a bead on the location of a gene crucial in a large majority of the cancers, especially the hereditary cases that make up about 10% of all melanomas.

Pinpointing the actual gene could take years, and there is a debate over whether it is the only gene that predisposes to melanoma, but the new research has buoyed investigators' hopes. "What's exciting [about these latest observations] is that this is a tumor where there is great potential for disease prevention and control," says oncologist Mark Green of the Mayo Clinic in Scottsdale. "This is a disease where we can clearly win, and unraveling the genetics is extremely important." That task is becoming ever more urgent since the incidence rate for melanoma has risen faster than that of any other cancer except lung cancer. Each year, more than 32,000 Americans contract melanoma and nearly 8000 die annually from it, despite the fact that the cancer is rarely fatal if detected and treated early. Researchers are hoping that this latest research will lead to a genetic test that could be used to warn those predisposed to the disease to avoid the sun and check their skin frequently. In the long run, identifying genetic abnormalities involved in melanoma could lead to new therapeutic strategies.

Implicating chromosome 9. Lisa Cannon-Albright and Mark Skolnick.

For the past half-decade or so, the search for melanoma genes has been largely a tale of three chromosomes, specifically the short arms of chromosomes 1 and 9 and the long arm of chromosome 6. In the late 1980s, investigators began trying to nail down the location of a hereditary melanoma gene by conducting genetic linkage studies in families with a history of melanoma and dysplastic nevi—pigmented moles that in some cases appear to be tumor precursors. These studies seemed to hit paydirt in 1989 when Green, then at the National Cancer Institute (NCI), and collaborators from NCI, the Massachusetts Institute of Technology (MIT), the University of Pennsylvania, and Collaborative Research Inc., published a landmark study in *The New England Journal of Medicine* that provided evidence that a gene on chromosome 1 was linked to hereditary cases of melanoma.

Shifting focus. In the years since, however, a number of other groups, using different sets of families, have obtained contradictory results that find no indication of linkage to chromosome 1. These results prompted a sometimes bitter debate between members of Green's collaboration and some of the opposing groups over whether the findings were skewed by differences in the sizes of the families studied or by differences in the families' sun exposure—a factor that could affect the incidence of noninherited sporadic melanoma. Most important, the chromosome 1 issue became mired in a controversy over the relevance of dysplastic nevi to melanoma and the diagnostic criteria used to identify the moles. "It led to a great deal of acrimonious back and forth that plagued the field and clearly slowed work in the area," recalls Green. "Interest began to wane in looking at that part of chromosome 1." As a result, while some researchers, such as the NCI group, continued to pursue a chromosome 1 gene, and still do so today, a number of other investigators began to explore other areas of the genome like chromosome 6, where data suggest there is a gene that acts late in the cancer progression.

In the last year or so, however, the melanoma spotlight has shifted to chromosome 9, when three lines of evidence converged to implicate a region called p21 that lies in the middle of the chromosome's short arm. Some of the earliest hints pointing to that site came